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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,562	03/22/2006	Fokke Venema	9310-150	3570

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
03/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,562	VENEMA, FOKKE	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/12/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-38,40,41,43,44,47-52 and 54-56* is/are pending in the application.

4a) Of the above claim(s) *20-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41,43,44,47-52 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/3/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed January 12, 2009. This action is made FINAL.

Claims 20-38, 40-41, 43-44, 47-52, and 54-56 are currently pending. Claims 40, 41and 44 have been amended. Claim 56 is newly presented. Claims 20-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Withdrawn Objections

2. The objection made to the specification in section 2 of the Office Action of September 11, 2008 is withdrawn in view of the amendments made to the specification.

The objection made to claim 44 in section 3 of the Office Action of September 11, 2008 is withdrawn in view of the amendments made to the claims.

Withdrawn Rejections

3. The rejections made under 35 USC 112 2nd paragraph in section 4 of the Office Action of September 11, 2008 are withdrawn in view of Applicants arguments and amendments made to the claims.

The rejections made under 35 USC 102 in section 5 of the Office Action of September 11, 2008 are withdrawn in view of amendments made to the claims.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a new rejection necessitated by amendment:

Claims 40, 44, 47, 54, and 56 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Beckman (US 2003/0134307 Pub 7/2003 and filed 10/2002).

Regarding Claims 40 and 56 Beckman teaches molecular beacon (MB) probes comprising modified nucleotides. Specifically Beckman teaches that a MB probe comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5'end) (para 0074). In the instant case since the 5' end of the MB probe would be part of the stem region, Beckman exemplifies an MB probe comprising a stem comprising one 2'-O-methyl nucleotide and one or more unmodified nucleotides. Additionally Beckman exemplifies a probe wherein each base pair of the stem comprises no more one 2'-O-methyl nucleotide (since Beckman exemplifies that the 2'-O-methyl nucleotide is only present at the 5'end of the MB probe and the base pairs of the stem region are formed via the hybridization of the 5' and 3' ends). Further

it is an inherent property of this probe that it has better stability and does not open spontaneously in the presence of contaminants present in an amplification enzyme mixture comprising said molecular beacon probe compared to a molecular beacon probe without said stem.

Regarding Claim 44 Beckman teaches a MB probe wherein the 2'-O-derivatized nucleotide is a 2'-O-methyl nucleotide (para 0074).

Regarding Claim 47 Beckman teaches that a MB probe comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5'end) (para 0074). In the instant case the 5' end of the MB probe would be part of the stem region and Beckman teaches that the stem regions are usually 3-25 nucleotides in length (para 0097). Therefore if the 5' end of the MB probe contained a single 2'-O-methyl nucleotide than the 5' end of the MB probe would also have 2-25 standard deoxyribonucleotides that would base pair with standard deoxyribonucleotides at the 3' end of the MB probe since Beckman exemplifies a MB probe having a 2'-O-methyl nucleotide only at the 5'end. Thus Beckman exemplifies a MB probe wherein at least one base pair constituting the stem contains no nucleotide or nucleotide analogue having an affinity increasing modification.

Regarding Claims 54 Beckman teaches a kit comprising primers, polymerase, reagents for performing amplification of an analyte, and a molecular beacon (para 0086).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a new rejection necessitated by amendment:

Claims 41, 43, 48-52, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beckman (US 2003/0134307 Pub 7/2003 and filed 10/2002) as evidenced by Majlessi (Nucleic Acids Research 1998) and Tsourkas (Nucleic Acids Research 2002).

In addition to the teachings of Beckman presented above Beckman teaches that a MB probe can comprise one or more 2'-O-methyl nucleotides or a MB probe can consist entirely of 2'-O-methyl nucleotides (para 0074).

Beckman does not specifically teach a MB probe wherein said loop comprises one or more 2'-O-methyl nucleotides wherein the sensitivity of said probe to polymorphisms in the target nucleic acid sequence is lowered as compared to a MB probe without said loop (clm 41). Additionally Beckman does not specifically teach a MB probe wherein one base pair constituting the stem contains no 2'-O-methyl nucleotide (clms 49 and 50). Beckman does not specifically teach a MB probe wherein each strand constituting the stem contains at least one 2'-O-methyl nucleotide (Clms 51 and 52). Further Beckman does not specifically teach a kit comprising a MB probe as claimed in claim 41 (clm 55).

While Beckman does not exemplify each and every probe recited by the claims designing probes which are equivalents to those being claimed is considered routine experimentation especially since MB probes comprising standard deoxyribonucleotides and one or more 2'-O-methyl nucleotides had already been described by Beckman. Further the advantages of using probes comprising 2'-O-methyl nucleotides were already known. Specifically Majlessi teaches that 2'-O-methyl oligoribonucleotide probes afford multiple advantages over 2' deoxy oligoribonucleotide probes for detecting RNA targets, including greatly increased Tm which allows use of shorter probes, faster kinetics of hybridization, ability to bind to structured targets under conditions where 2' deoxy oligoribonucleotide probes will not and significantly improved specificity. Majlessi further states that these advantages render 2'-O-methyl oligoribonucleotide probes superior to 2' deoxy oligoribonucleotide probes for use in assays that detect RNA targets (page 2224 and 2229). Additionally Tsourkas teaches that 2'-O-methyl oligoribonucleotides bind RNA with higher affinity and faster kinetic hybridization rates, resist nuclease degradation, and do not form a substrate fro Rnase H. Tsourkas further teaches that 2'-O-methyl MB probes form a more stable stem-loop structure because of the presence of the 2'-O-methyl nucleotides. In the absence of target, the 2'-O-methyl MB exhibited a higher Tm and a lower level of background fluorescence compared with the 2' deoxy MB. The 2'-O-methyl modification of the MB backbone resulted in a higher affinity for target mRNA. The melting temperature of the 2'-O-methyl/RNA hybrid was found to be significantly higher than that of the 2'-deoxy/RNA hybrid (page 5173). Thus the benefits of using modified probes were well known in the art at the time of the

invention. Although Majlessi and Tsourkas compared probes consisting of 2'-O-methyl oligoribonucleotides to probes consisting of 2' deoxy oligoribonucleotides one of skill in the art would have recognized that probes consisting of both 2'-O-methyl nucleotides and 2' deoxy oligoribonucleotides would also be useful. Thus the prior art is replete with guidance and information necessary to permit the ordinary artisan to design MB probes that have better stability and do not open spontaneously (because the stem region comprises 2'-O-methyl nucleotides) and probes that are more sensitive to polymorphisms (because the loop region comprises 2'-O-methyl nucleotides). Based on the computer programs available an ordinary artisan would have had more than a reasonable expectation of success of designing the probes that have better stability and do not open spontaneously and probes that are more sensitive to polymorphisms. Thus, for the reasons provided above, the probes of the instant invention would have been obvious to one of ordinary skill in the art.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634